Organic Process Research & Development **2010,** *14,* 1512–1517

Optimization of a Hydrogenation Process using Real-Time Mid-IR, Heat Flow and Gas Uptake Measurements

Benjamin J. Littler,* Adam R. Looker,† and Todd A. Blythe†

Vertex Pharmaceuticals, Inc., 11010 Torreyana Road, San Diego, California 92121, United States, and Vertex Pharmaceuticals, Inc., 130 Waverly Street, Cambridge, Massachusetts 02139, United States

Abstract:

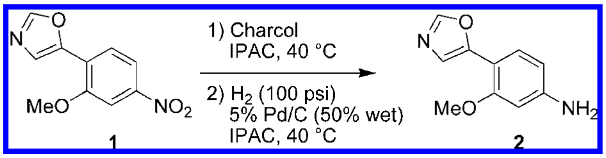
This paper describes using real-time mid-IR, heat flow, and gas uptake data to optimize the hydrogenation of a nitroaromatic to an aniline that had been difficult to control during a previous campaign in the pilot plant. A bimetallic Pt/V catalyst was identified that eliminated the buildup of reaction intermediates and consequently resulted in an inherently more controllable process. The real-time analytics were then used to rapidly optimize the reaction conditions and develop strategies for controlling the reaction rate in the plant should an unexpected deviation occur.

The FDA's PAT initiative[1] and ICH Guideline Q8/Q8(R)[2] promote using real-time analytics to develop process understanding and fundamentally robust chemical processes. At Vertex Pharmaceuticals we have incorporated many real-time analytical instruments into our Chemical Development team and have found that, with a few hours of basic training, organic chemists who are not experts in real-time analytics are able to acquire extremely useful semi-quantitative data that they can use to develop inherently better processes. A few more experienced users for each instrument are needed to help train the rest of the team and run the more demanding applications. Ideally, the level of process understanding gained in the laboratory is sufficient to allow us to run our processes safely in the plant without real-time analytical tools being present since their introduction is typically expensive, time-consuming, and technically demanding and requires additional ongoing maintenance.

This paper describes optimizing the catalytic hydrogenation of aromatic nitro compound **1** to aniline **2** with the use of a commercial hydrogenation system that had been modified to accommodate a mid-IR probe and linked to data-recording software to provide real-time heat flow and gas uptake measurements.

The reaction conditions shown in Scheme 1 were developed using a metal pressure vessel with no online monitoring of the reaction other than an analog pressure gauge and a digital thermocouple. A standard Pd/C catalyst gave clean conversion to the desired product, and the reaction exotherm was readily controlled in the laboratory. Consequently, the process was transferred to the pilot plant. As detailed previously the transfer of the process was not straightforward,[3] and in some of the batches performed it proved difficult to control the reaction exotherm. The aims of the development work described in this paper were to understand why the initial process was difficult to control and then to develop an inherently more robust process that could be run safely in the pilot plant.

Scheme 1. **Initial reaction conditions developed without PAT tools**



Three factors were identified as likely causes for the difficulty controlling the exotherm in the initial plant campaign.

(1) Batches of **1** showed variable activity in the hydrogenation: highly colored batches typically required significantly more catalyst than lightly colored batches. Despite significant analytical efforts it was not possible to conclusively identify any impurities that were causing the variability in reactivity. In the laboratory, pretreatment of a solution of **1** with activated charcoal generally made all batches similarly reactive as best as we could tell using our standard hydrogenator without PAT tools, but in the plant it was found that the use of a single reactor with circulating loop was ineffective at removing all of the charcoal, and a slow reaction occurred. As a result, the next batch was filtered between two reactors to ensure all of the charcoal was removed, but this led to an unexpectedly fast reaction that was difficult to control.[3] The initial use of the automatic system described in this paper was simply to use-test batches of **1** under reaction conditions that could be precisely reproduced and the reaction rate accurately quantified, so that batches that reduced slowly were rejected from our suppliers before being shipped to the plant. This use-testing allowed us to eliminate the complex charcoal treatment from the plant procedure for subsequent plant campaigns.

(2) Nitroaromatic **1** is only partially soluble in isopropyl acetate (IPAC) under the reaction conditions so that the initial heat output of the reaction is counterbalanced by the enthalphy of dissolution of **1**. Any increase in temperature will dissolve more solid, allowing more material to react; conversely, a decrease in temperature will retard the dissolution of **1**, thus shutting the reaction down. In both cases a feedback loop is

---

* Author for correspondence. Email: benjamin_littler@sd.vrtx.com. Telephone 858 404 8464. Fax 858 404 6719.

† Vertex Pharmaceuticals, Inc., 130 Waverly Street, Cambridge MA 02139, USA.

(1) http://www.fda.gov/Cder/OPS/PAT.htm.

(2) http://www.ich.org.

(3) Looker, A. R.; Littler, B. J.; Blythe, T. A.; Snoonian, J. R.; Ansell, G. K.; Jones, A. D.; Nyce, P.; Chen, M.; Neubert, B. J. *Org. Process Res. Dev.* **2008**, *12*, 666.

10.1021/op100169j

Figure 1. **Introduction of the mid-IR probe into the hydrogenation vessel.**

set up that tends to reinforce the direction that the reaction temperature is headed.

(3) Aromatic nitro reductions can be complex multistep processes with the individual steps having different rates leading to the buildup of intermediates that can then react with strong exotherms.[4] HPLC analysis of the initial reaction conditions confirmed the buildup of significant quantities of the reaction intermediates;[3] accordingly, the heat output depended on the extent of the reaction.

In order to gain greater process understanding we used a more advanced commercially available hydrogenation system that accurately controlled the gas pressure, rate of stirring, reaction temperature, and rate of gas addition. The system was connected to a computer to log, process, and compare data from experiment to experiment. The physical variables recorded by the system were rate of gas uptake, rate of stirring, volume of gas consumed (extent of reaction), and heat flow ($T_r - T_j$; the difference between the reaction temperature and the circulator fluid temperature). To correlate the physical measurements with the chemical changes in the reactor, we introduced a mid-IR probe through the vessel head as shown in Figure 1.

Observations made during the course of our research using this experimental setup included the following:

- A mirrored optical conduit was needed to observe the entire mid-IR region from 4000 to 600 cm^{-1} in order to detect intermediates containing OH and NH bands between 4000 and 3000 cm^{-1}.[5] Fiber-optical paths are increasingly preferred for mid-IR spectroscopy since they can be readily cleaned between experiments without optical realignment but are not suitable for this application because the fiber absorbs radiation above 1900 cm^{-1}.[6] We found that the inconvenience of using the mirrored optical system was minimal since it could be readily realigned in less than 5 min, provided that the arm was kept in approximately the same orientation during cleaning.
- Better data were obtained using a probe with a silicon window (SiComp) rather than a diamond window (DiComp). The diamond window is often preferred by chemists for general use because it is more chemically robust under strongly basic conditions. This reaction was run at neutral pH, so we used the silicon-based window because it has a wider spectral window and gives a better signal-to-noise ratio.[7]
- The ReactIR probe had to be removed from the reactor between each experiment and the optical window physically cleaned in order to obtain the highest quality data. Attempted in situ cleaning of the probe window in the reactor using stirred solvents was unsuccessful; a residue gradually built up that led to broad low-intensity bands in the IR spectra.
- The 17-mm mid-IR probe could only fit through the single wide port in the metal reactor head initially designed to charge the reagents and solvents to the vessel. In order to get the best possible data, a new background spectrum had to be acquired before each experiment; therefore, the mid-IR probe was placed first into the empty vessel, and then the reaction chemicals were added through one of the narrower ports using a narrow bore plastic funnel. This required that solids added (nitroaromatic **1** and catalyst) be free of lumps and carefully washed into the vessel by the solvent.
- A PTFE Swagelok fitting is preferred for coupling the mid-IR probe to the metal reactor head. A Hastelloy metal fitting used initially became scratched and deformed over time and started to leak. Removing the metal fitting from the probe required special tools and significant care not to deform the probe. The PTFE fitting was readily removed and adjusted between runs, and prevented gas leakage up to the 6 bar pressure limit of the glass vessel.
- A reaction volume of at least 100 mL is required for the mid-IR probe to be fully immersed in the 250-mL glass vessel, so the system is best suited for optimization when raw materials are plentiful. However, since each experiment performed is rich in data, we also use the system in early development to verify that conditions identified by small-scale screening experiments are suitable for scale-up.
- Mid-IR spectroscopic bands are typically well resolved so that the concentration of the chemical species present can be readily determined by measuring the peak height relative to a nearby baseline region that contains no peaks. This peak profiling analysis is readily understood by organic chemists and is performed in real-time by the instrument software so that training for nonspecialist users is minimal. More advanced chemometric modeling based on a principal component analysis can be completed by power users if required, but we have found that for analyzing the major changes in most hydrogenation reactions it is not needed.

Figures 2 and 3 show waterfall plots of mid-IR spectra acquired every 2 min under the initial reaction conditions shown in Scheme 1. Four mid-IR bands can be readily correlated to chemical species in the reaction mixture: 1530 cm^{-1} (aromatic nitro group in starting material **1**), 1620 cm^{-1} (NH in hydroxyl-

---

(4) Baumeister, P.; Blaser, H.-U.; Studer, M. *Catal. Lett.* **1997**, *49*, 219.
(5) http://en.wikipedia.org/wiki/Infrared_spectroscopy.
(6) Minnich, C. B.; Buskens, P.; Steffens, H. C.; Bäuerlein, P. S.; Butvina, L. N.; Küpper, L.; Leitner, W.; Liauw, M. A.; Greiner, L. *Org. Process Res. Dev.* **2007**, *11*, 94.
(7) Mettler Toledo AutoChem, Inc., 7075 Samuel Morse Drive, Columbia, MD 21046, United States.

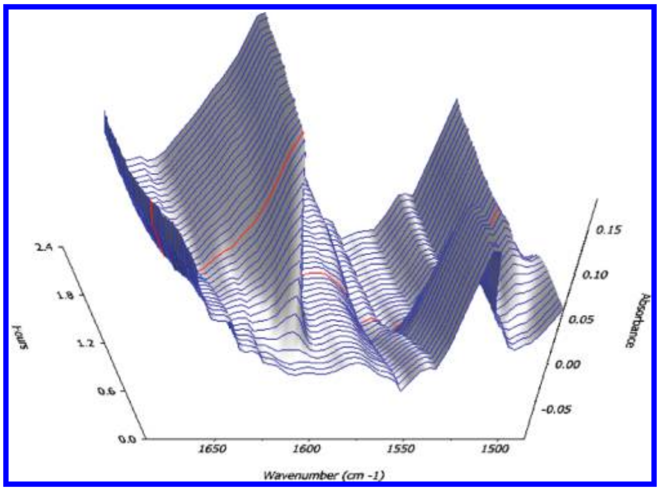


Figure 2. **Waterfall plot of mid-IR spectra 1475 to 1675 cm^{-1}.**

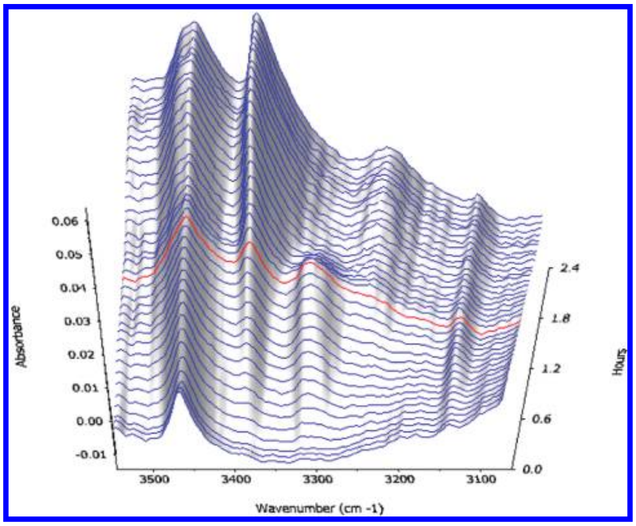


Figure 3. **Waterfall plot of mid-IR spectra 3075−3525 cm^{-1}.**

amine intermediate **3** and aniline product **2**), 3310 cm^{-1} (OH in hydroxylamine intermediate **3**), and 3380 cm^{-1} (NH$_2$ in product **2**).[5,8] The spectrum acquired at 70 min highlighted in red in both Figures 2 and 3 corresponds to the maximum accumulation of the hydroxylamine intermediate.

Figure 4 shows the heat flow from the initial reaction conditions and the peak profiles extracted from the mid-IR data presented in Figures 2 and 3. These data reveal a lot of information about the complexity of the reduction process. The initial phase of the reaction up to 50 min shows a relatively constant level of nitro compound **1** (red line, 1530 cm^{-1}) because the material is not fully dissolved at the start of the reaction. During the first 50 min there is a steady increase in the heat flow (black line) corresponding to the buildup of the hydroxylamine intermediate **3** (green line, 3308 cm^{-1}). The exotherm reaches a maximum at about 70 min; at which point all of nitroaromatic **1** is consumed and the hydroxylamine level is at its maximum. The exotherm then decreases as the hydroxylamine intermediate is consumed.

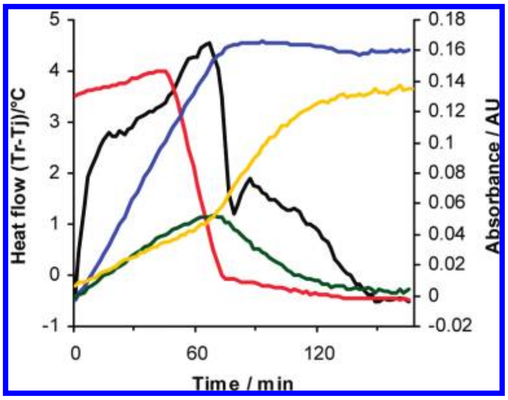


Figure 4. **Peak profiles and heat flow of initial reaction conditions. heat flow (black); mid-IR bands 1530 cm^{-1} (nitroaromatic 1, red), 1620 cm^{-1} (aniline 2 and hydroxylamine 3, blue), 3310 cm^{-1} (hydroxylamine 3, green), 3380 cm^{-1} (aniline 2, gold).** ***Note: the absorbance of the bands at 3308 and 3381 cm^{-1} have been multiplied by a factor of 5.***

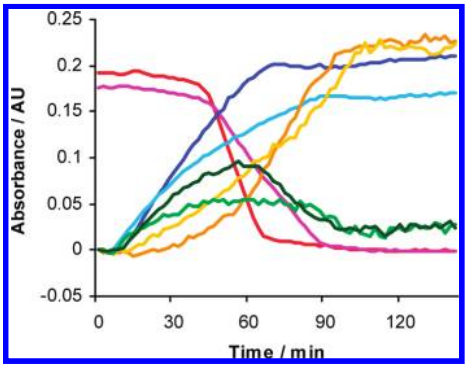


Figure 5. **Effect of lowering the hydrogen pressure from 5 bar to 1 bar. Mid-IR bands 1530 cm^{-1} (nitroaromatic1, 5 bar red, 1 bar pink), 1620 cm^{-1} (aniline 2 and hydroxylamine3, 5 bar dark blue, 1 bar light blue), 3310 cm^{-1} (hydroxylamine 3, 5 bar dark green, 1 bar light green), 3380 cm^{-1} (aniline 2, 5 bar gold, 1 bar orange).** ***Note: the absorbance of the bands at 3310 and 3380 cm^{-1} have been multiplied by a factor of 5.***

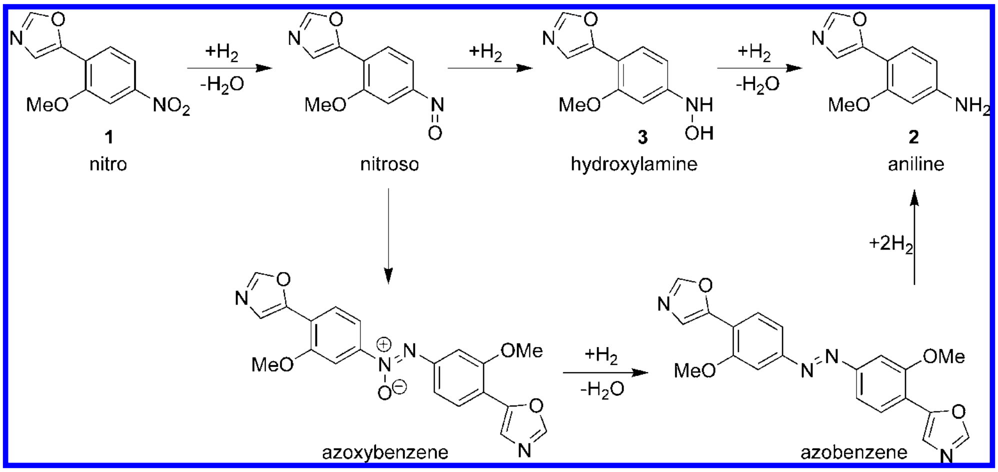
The pilot-plant vessel was relatively empty and pressurized to 5 bar overpressure, and we believed that the large quantity of hydrogen in the system made the exotherm harder to control. We decided that the optimized reaction conditions should be at 1 bar overpressure in order to limit the amount of hydrogen available to the system in the event of a loss of control. Figure 5 shows that the lower pressure had minimal effect on the overall reaction time, and so all subsequent experiments were performed at 1 bar overpressure.

Dual-metal catalysts have been developed to minimize the buildup of the hydroxylamine intermediate in aromatic nitro group reductions.[4] A heavy metal, typically Pd or Pt, performs the conventional catalytic cycle, and a first-row transition metal, typically Fe or V, catalyses the disproportionation of the hydroxylamine intermediate to the aniline and nitroso compounds (Scheme 2). Three dual-metal catalysts recommended by a commercial vendor for aromatic nitro reductions were screened. Figure 6 shows that two of the three dual-metal catalysts formed the aniline approximately as rapidly as the Pd/C catalyst, while the third catalyst was far less effective. More importantly Figure 7 shows that the band at 3310 cm^{-1}, characteristic of the hydroxylamine intermediate, was hardly

---

(8) An experiment was performed where samples were removed approximately every 15 min for HPLC analysis. This confirmed that that the changes in the mid-IR bands measured from peak height to baseline correlated to the chemical transformations under investigation.

Scheme 2. **Mechanism for the conversion of nitroaromatic 1 to aniline 2**



detected for catalyst CF-1082 and that the heat flow profile was steady throughout the course of the reduction. The three catalyst screening reactions were performed on the same day, illustrating how the data-rich experiments performed with this system allowed rapid identification of an inherently more robust catalyst for performing the reaction on large scale. Catalyst CF-1082 consisting of 1% Pt and 2% V on carbon was used exclusively in all of the following studies.[9]

Our next goal was to determine the optimal catalyst loading. Figure 8 shows that the initial 1% catalyst loading gave an unacceptably slow reaction rate; therefore, an additional 1% of catalyst was added to the reactor after approximately 60 min, and then the reaction proceeded at an acceptable rate. A 2% loading of catalyst was used for all subsequent experiments. This example illustrates how real-time analytical data can be used to monitor and adjust an experiment faster than if off-line analysis is used. Although the cost per gram of Pt is approximately 5 times that of Pd,[10] the overall metal cost of a 2% loading of 1% Pt is approximately 3 times less than a 4.5% loading of 5% Pd. Analysis of the isolated aniline **2** using ion-coupled plasma mass spectrometry showed less than 1 ppm of residual Pt.

The real-time data allowed us to probe the effect of the stirrer speed on the rate of the reaction in a single experiment that is shown in Figure 9. The reactor system contains a hollow turbine that achieves good mass transfer of the gas into solution by drawing fine bubbles of gas into the reaction solution at speeds above approximately 450 rpm. The first 60 min of the experiment was performed under conditions of poor gas mass transfer by setting the stirrer speed to 200 rpm. The increase of the band at 1620 cm^{-1} shows that product **2** is formed more slowly under these conditions than when the stirring speed is increased to 500 rpm (good mass transfer) after 60 min. At 120 min the stirrer speed was increased further to 1000 rpm, but the rate of product formation was essentially unchanged. At 180 min the stirrer was slowed again to 200 rpm, and the rate of reaction slowed again to its initial rate. At 300 min the rate was increased to 500 rpm, and the reaction rate increased again. The heat flow profile also follows the changes in the

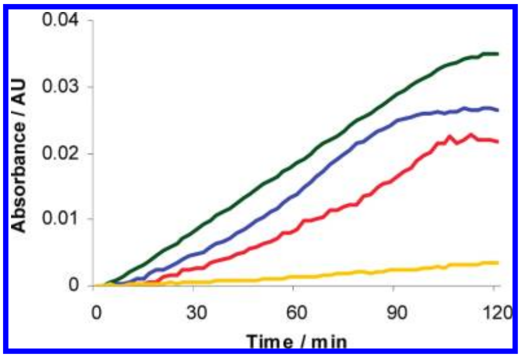


Figure 6. **Intensity of the aniline 2 mid-IR band at 3380 cm^{-1} during the catalyst screen. Pd/C (red), CF-105 (blue), CF-1082 (green), CE-1097 (gold).**

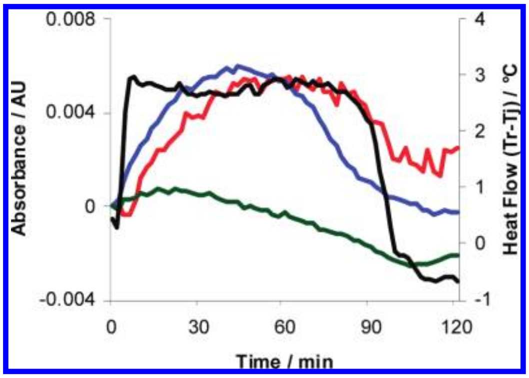


Figure 7. **Hydroxylamine 3 band at 3310 cm^{-1} during catalyst screen and heat flow for catalyst CF-1082. Heat flow (black). Mid-IR bands; Pd/C (red), CF-105 (blue), CF-1082 (green).**

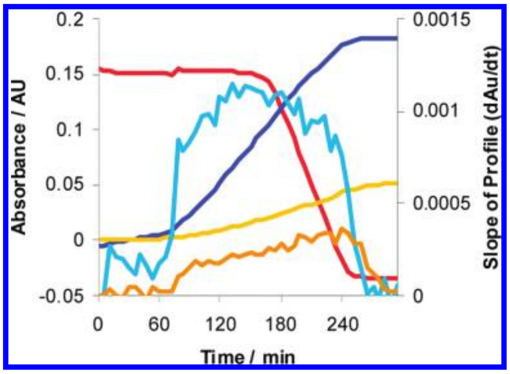


Figure 8. **Optimization of the catalyst loading. Mid-IR bands 1530 cm^{-1} (nitroaromatic 1, red), 1620 cm^{-1} (aniline 2, dark blue), 3310 cm^{-1} (aniline 2, gold), first derivative of band at 1620 cm^{-1} (light blue), first derivative of band at 3310 cm^{-1} (orange).**

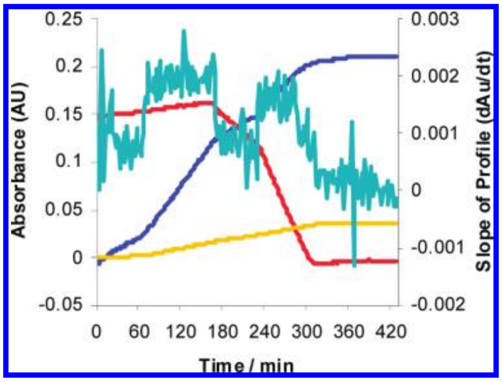


Figure 9. **Effect of stirrer speed. Mid-IR bands 1530 cm^{-1} (nitroaromatic1, red), 1620 cm^{-1} (aniline 2, dark blue), 3308 cm^{-1} (aniline 2, gold), first derivative of band at 1620 cm^{-1} (light blue).**

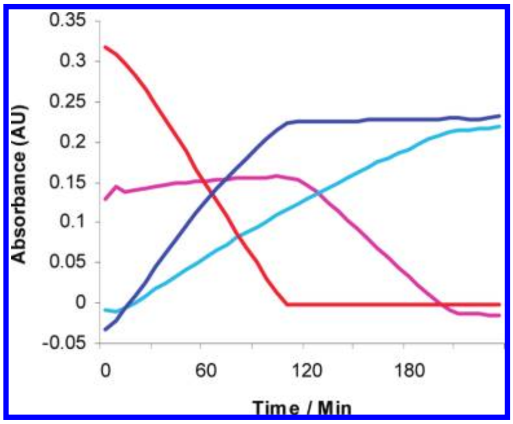


Figure 10. **Effect of temperature. Mid-IR bands 1530 cm^{-1} (nitroaromatic1, 80 °C red, 40 °C pink), 1620 cm^{-1} (aniline 2, 80 °C dark blue, 40 °C light blue).**

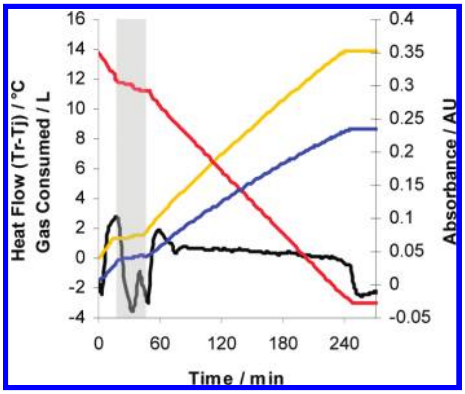
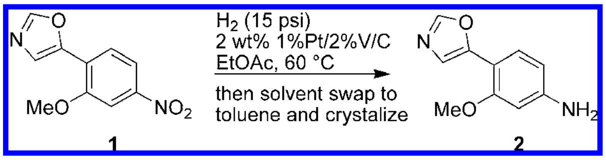


Figure 11. **Effect of hydrogen starvation. Heat flow (black); gas consumed (gold); period of hydrogen starvation (gray); mid-IR bands 1530 cm^{-1} (nitroaromatic1, red), 1620 cm^{-1} (aniline 2, blue).** ***Note: both heat flow and gas uptake are plotted on the left-hand y-axis. The units are °C for heat flow and L for gas uptake.***

Scheme 3. **Optimized procedure for the conversion of nitroaromatic 1 to aniline 2**



stirrer speed, demonstrating that a runaway reaction in the plant could be controlled simply by slowing or turning off the stirrer.

Next we examined the effect of performing the reaction at 80 °C rather than 40 °C because a solubility study showed that nitroaniline **1** was fully dissolved in 10 L/kg IPAC at 80 °C. The immediate drop in the IR band at 1530 cm^{-1} at 80 °C in Figure 10 shows that the temperature increase afforded a faster reaction. An unexpected added benefit of the higher temperature was that the product solution was noticeably less colored: orange in color at 40 °C but pale yellow at 80 °C. It was noticed that the orange color resulted in the formation of highly colored solid particles during the isolation of aniline **2** by precipitation with *n*-heptane in the previously reported plant procedure.[3] A screen of solvents revealed that aniline **2** recrystallized cleanly from toluene with the colored material remaining in solution. We felt that incorporating a full recrystallization at this stage would afford the API with consistently higher quality since nitroaromatic **1** was a raw material that we purchased from a number of vendors and aniline **2** was the final intermediate before our API. We therefore decided to perform the reaction in EtOAc (bp 77 °C) since the solvent swap to toluene (bp 110 °C) would be faster than if IPAC (bp 87 °C) were the reaction solvent. We decided to run the reaction at 60 °C in EtOAc since the nitroaromatic **1** was fully dissolved at this temperature and we did not want to run above the solvent boiling point. Previous studies at 40 °C had shown no significant difference in reaction rate between reactions run in IPAC and EtOAc.

Finally, we looked at the effect of hydrogen starvation on the reaction since shutting off the hydrogen could provide a highly effective method to stop a reaction that was running out of control. As shown in Figure 11 we performed a reaction where we waited for the difference in the reaction and jacket temperatures to reach a maximum (about 20 min), then we shut the hydrogen inlet. The ReactIR profiles and the heat flow data show that the reaction rate decreased rapidly. When the hydrogen inlet was reopened (50 min), the reaction immediately restarted at the same rate as before the inlet was shut. We therefore knew that we could prevent an exothermic runaway by shutting off the hydrogen supply to the vessel.

The hydrogen gas uptake data show a close correlation to the mid-IR data so that our plan was to monitor gas uptake using existing equipment in the plant to follow the reaction progress rather than install a mid-IR probe or pull multiple samples for off-line HPLC analysis. A single off-line HPLC sample would be taken approximately 1 h after gas uptake had stopped to verify that the reaction was complete.

The optimized procedure, summarized in Scheme 3, was successfully completed a number of times on up to a 100-g scale in the laboratory to afford **2** in 91% yield and 100% AUC by HPLC, but unfortunately the project was deprioritized just prior to implementing the improved process in the pilot plant. Importantly, the process understanding gained in the laboratory allowed the team to develop a plan that was written into the plant batch record for how to cope with an unexpectedly exothermic reaction: the hydrogen inlet valve would be shut and the stirrer stopped.

---

(9) HPLC analysis of the final product mixture showed much cleaner conversion of **1** to **2** compared to using the Pd/C catalyst.

(10) Platinum: $1220.90/Troy oz; palladium $238.50/Troy oz NYMEX Close April 15, 2009.

Conclusion

The experimental equipment detailed in this paper has been used in a number of subsequent programs to develop a range of hydrogenation processes in the lab. In all cases the transfer to the plant occurred smoothly, demonstrating the utility of making real-time analytical systems readily available to the organic chemists in the Research and Development laboratories. Over the past few years we have found that nonexpert users can readily apply a range of real-time analytical techniques to develop fundamentally good processes in the laboratory that transfer readily to the pilot plant, freeing our experts in real-time analytics to focus their efforts on developing and installing fewer but more complex validated systems required for commercial manufacturing.

Experimental Section

All chemicals were used as received from commercial suppliers. Nitroaromatic **1** was supplied by Asymchem, Nippon Soda, Daito and Nippon Ghosei. Pd/C was supplied by Engelhard, and the bimetallic catalysts were supplied by Degussa. All catalysts used were supplied and used containing approximately 50% water. The loadings quoted are the calculated dry loading in g/g relative to nitroaromatic **1**. The optimization experiments were performed using a Büchi Ecoclave hydrogenation system equipped with a 250-mL glass vessel. The stirrer consisted of a hollow, flat blade turbine constructed of Hastelloy and was powered by a Cyclone 075 motor. The minimum stir speed required to draw gas down into the solution (450 rpm) was determined by gradually increasing the stirrer rate until fine gas bubbles were observed in a solution of isopropyl acetate at 20−25 °C. The reactor head was fabricated from Hastelloy and contained seven ports. A rupture disk rated to 6 bar was attached to the vessel. Gas was introduced to the system via a bpc 1210 unit (Büchi). The reaction temperature was measured using a Pt 100 thermocouple. A Huber 340W Unistat was used to control the reaction temperature. The stirrer motor speed (Cyclone 075 motor), volume of gas absorbed (bpc 1210 unit), rate of gas absorption (bpc 1210 unit), reaction pressure (pressure transducer), reaction temperature (Pt100 thermocouple) and circulator fluid temperature (Huber 340W Unistat) data feeds were connected to a Büchi bds mc unit that was in turn connected via an RS-232 connection to a PC running the Büchi "Look and See" software with a data sampled once every 100 s. Data analysis was performed by exporting the Büchi "Look and See " file to Microsoft Excel. The heat flow was calculated by subtracting the fluid temperature from the reaction temperature. Triply insulated piping was used to connect the reactor to the Huber circulator to minimize the heat flow other than through the glass reaction vessel. Mid-IR spectra were collected using a Mettler Toledo ReactIR 4000 system equipped with a six-mirror optical conduit and Si-comp probe. The Si-comp probe was introduced into the 1/2-in. NPT port of the hydrogenator using a PTFE Swagelok fitting. The Swagelok ring was placed on the probe so that the probe was approximately 1 mm away from the side wall of vessel. This afforded a minimum reaction volume of approximately 100 mL to completely cover the window of the mid-IR probe. Mid-IR spectra were recorded every 2 min using ReactIR control software, version 3.0 (Mettler Toledo). Mid-IR data were exported to Microsoft Excel and combined with the Buchi "Look and See" data. Before each experiment the Si-comp probe was removed from the reactor and carefully cleaned using a cotton bud soaked in acetone until the gray residue from the previous experiment had been fully removed. The reactor was cleaned between experiments using methanol followed by water followed by acetone. The reactor was then flushed with nitrogen for approximately 30 min until all of the solvent evaporated. The mid-IR probe was then introduced into the reactor, the optical path aligned, and the background reference spectrum obtained. Solid nitroaromatic **1** was then added to the reactor followed by the catalyst. The system was flushed with nitrogen one more time, and then the solvent was added. The system was sealed, the stirrer was set to 500 rpm and then pressurized three times with nitrogen to ensure an inert atmosphere. The stirrer was then slowed to approximately 100 rpm as the reaction mixture was heated to the desired temperature. Once the desired reaction temperature was achieved, the stirrer was stopped, and the reactor headspace was pressurized three times with hydrogen. The reaction was then initiated by starting the stirrer. At the end of the reaction the hydrogen atmosphere was released, and the system was pressurized three times with nitrogen before being drained. The product mixture was then filtered through a pad of Celite under a nitrogen blanket to remove the catalyst, and the solution was analyzed by HPLC to verify complete conversion of **1** to **2**.

3-Methoxy-4-(oxazol-5-yl)aniline (2). 5-(2-Methoxy-4-nitrophenyl)oxazole (**1**) (1.00 equiv) and 1% Pt, 2% V on C (64% wet, 2.0 wt % on a dry basis) are charged to a hydrogenation vessel under nitrogen. EtOAc (10 vol) is added, and the mixture is heated to 60 °C. The vessel is pressurized with hydrogen (1.00 bar overpressure), and the mixture is stirred at 60 °C. The reaction is typically complete within 3 h. The pressure is released, and nitrogen is bubbled through the reaction mixture. The reaction mixture is filtered through Celite and washed with EtOAc (2 vol). The solvent level is reduced to 4 vol by distillation at reduced pressure, and toluene (10 vol) is charged into the vessel. The solvent level is reduced to 4 vol by distillation at reduced pressure, and a second portion of toluene (10 vol) is charged into the vessel. The solvent level is reduced to 5 vol under reduced pressure, and then the mixture is heated to 90 °C at atmospheric pressure to dissolve any solids. The solution is then cooled slowly to 20 °C to induce crystallization. The solid is isolated by filtration, washed with toluene (2 vol), and then dried in a vacuum oven at 50 °C with a nitrogen bleed until a constant weight is attained to afford 3-methoxy-4-(oxazol-5-yl)aniline (**2**)[3] as a pale-yellow solid (91% yield, 100% AUC by HPLC).

Received for review June 16, 2010.

OP100169J